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09/425,742	10/22/1999	KARL THEODOR KRAEMER	DEAV1998/L071 US NP	9957
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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP 901 NEW YORK AVENUE, NW WASHINGTON, DC 20001-4413			EXAMINER YU, GINA C	
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			1611	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary**Application No.**

09/425,742

Applicant(s)

KRAEMER ET AL.

Examiner

GINA C. YU

Art Unit

1611

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 February 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8, 10-23, 28, 29, 39-46 is/are pending in the application.
- 4a) Of the above claim(s) 3 and 41-45 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4-8, 11-23, 28, 29, 39, 40, and 46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SF/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Receipt is acknowledged of amendment and response filed on February 3, 2010.

Claims 1-8, 11-23, 28, 29, 39-46 are pending, of which claims 3, 41-44 have been withdrawn from consideration per species election according to Office action dated November 15, 2000.

Claim 45 is withdrawn from consideration as the claim (a) requires non-elected film forming agent. See 37 CFR 1.142(b) and MPEP § 821.03. Applicant has elected vinylimidazolium methochloride/vinylpyrrolidone copolymer. Therefore, claims 3, 41-45 are withdrawn from consideration; claims 1, 2, 4-8, 11-23, 28, 29, 39, 40, and 46 are examined on the merits.

Claim rejection made under 35 U.S.C. § 112, first paragraph as indicated in the previous Office action dated August 4, 2009 is withdrawn in view of applicant's remarks.

All claim rejections made under 35 U.S.C. § 103 (a) indicated in the same Office action are modified to address the claim amendment, but otherwise maintained for reasons of record.

Examiner duly notes that claim 39 was inadvertently omitted from the rejection statements. Since the Office action clearly has indicated that all claims examined on the merits were rejected and the claimed subject matter of claim 39 had been specifically addressed by discussing Smith (US 5658559) in the rejections, examiner views correction of this error would not cause a new Office action.

Also, as correctly pointed out by applicant, reference made to Example 15 in the previous discussion of Mougin should be made to Example 15. The correction is made in this Office action.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 4-8, 11-14, 22, 23, 28, 29, 39, 40 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaillard-Kelly (US 5411981 A) ("Gaillard") in view of Partain (US 4946870), Smith (US 5658559), and Mougin et al. (US 5753215 A) and Cremophor RH 40 Technical Information (1997).

Gaillard teaches that the phenylimidazolidines of instant formula I have anti-androgenic activity and are used in pharmaceutical compositions including creams, pomades, and lotions. See col. 9, lines 29 – 36. Example 96 teaches 4-[3-(4-hydroxybutyl)-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile. See instant claim 4. The reference teaches that the compositions useful for treatment of acne and androgenic alopecia, among others. See col. 9, lines 43 – 55.; instant claims 23 and 28. The reference specifically teaches that the compositions are "useful in dermatology" and can be used with other anti-acne components such as retinol or with a product stimulating the growth of hair such as Minoxidil (6-amino-4-4-piperidino-1, 2-dihydro-1-hydroxy-2-iminopyridimidine) for the treatment of alopecia. See col. 9, lines 56 – 65. See instant claims 11, 13, 23 and 28. Gaillard further

teaches adding to the composition 5 alpha-reductase inhibitor, which meets instant claims 16 and 17. See col. 9, lines 56 – 61.

Partain teaches a topical film-forming composition for delivering pharmaceutical actives with controlled release. The reference teaches that the composition is useful as a delivery system for single or combination of pharmaceutical active agents, including anti-acne agents (retinoic acid and benzoyl peroxide) and anti-alopecia agents (Minoxidil). See col. 9, lines 15 –16; Examples 1, 15, and 18. See instant claims 22, 23, 28, and 29. Partain also teaches using the delivery system for either single or combination of pharmaceutical agents. Particularly mentioned pharmaceutical actives are diazoxide, nifedipine and diltiazem; angiotensins (captopril). See col. 8, lines 55 – 58; col. 9, line 2; instant claims 11-14. The reference teaches that chitosan derivatives are useful film formers and topically applied in the form of lotion, solution, cream, etc. See col. 3, lines 28 – 52; instant claim 45. The polymer is said to readily form a film and “acts as a reservoir to continuously deliver the actives as well as protect the tissue from further injury or insult”, which negates the need of hair cover. The reference goes on to teach that the film gives uniform distribution of the active on the tissue and prevents the migration or loss of the active from the site of application, and helps to control the dosage at a constant level. The reference also teaches using solvents such as ethanol or and glycerin with the chitosan film-forming agent. See col. 9, line 58 –66; col. 10, lines 10-17; Example 14; instant claim 8.

Although Partain provides the general teaching of using a film-forming agent to formulate a controlled-release delivery system for anti-acne agents and anti-alopecia agents, either alone or in combination with other pharmaceutical agents, the reference does not mention the specific type of the film-forming polymer which the present applicant has elected for the prosecution.

Smith also teaches a film-forming lotion composition which forms barrier on the surface of the skin to prevent evaporative loss of moisture from the skin, and protects the skin from environmental irritants. The reference teaches polyquaternary polyvinylpyrrolidone such as polyquaternium-16 (polyvinylpyrrolidone/imidazolinium methochloride copolymers). See instant claims 40 and 46. Isopropanol is used as a solvent to dissolve pharmaceutical actives. See examples I and II; instant claim 8. The therapeutic agents include anti-acne actives including benzoyl peroxide and vitamin A. See col. 5, lines 1-6.

The references fail to teach the specific type of the elected plasticizer, polyoxyethylated hydrogenated castor oil.

Mougin teaches film-forming compositions for topical use. The reference teaches adding a plasticizing agent to the solution of the organic solvent in a proportion between 5-40% by weight relative to the weight of the film-forming polymer, for the purpose of improving the cosmetic and mechanical properties. See col. 5, lines 46 – col. 6, line 22. POE hydrogenated castor oil is among the possible

hydrophilic plasticizing agents. See also Example 16. The reference also indicates that isopropanol, which is used in Smith, is a volatile solvent. See col. 4, line 58.

Cremophor RH 40 Technical Information (Cremophor) teaches that POE hydrogenated castor oil is skin compatible and solubilizes hydrophobic pharmaceuticals including vitamin A (retinoic acid). See Solubilization. The reference teaches that the product forms clear solutions in water and ethanol with fatty acids and fatty alcohols. See Solubility.

Pertain and Smith would have obviously motivated one of ordinary skill in the art at the time the present invention to modify the teaching of Gaillard and formulate the active ingredients in a controlled-release composition because (a) Pertain teaches that a film-forming composition "acts as a reservoir to continuously and uniformly deliver the actives as well as protect the tissue from further injury or insult, which negates the need of hair cover, and controls the dosage at a constant level; (b) Smith also teaches a film-forming formulation which provides controlled-release of the actives while protecting the skin and prevent loss of moisture of the skin. The skilled artisan would have had a reasonable expectation of successfully producing a stable and effective film-forming lotion which is useful for treating acne or alopecia, and delivering the active agents in a controlled, constant dosage, while protecting the application site.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of the combined references by adding to the composition plasticizers such as POE hydrogenated castor oil as motivated by

Mougin and Cremophor because (a) Mougin teaches adding a plasticizer improves the cosmetic and mechanical properties of a film-forming topical compositions; and (b) Cremophor teaches that POE hydrogenated castor oil is a well known solubilizer in pharmaceutical/cosmetic art, which solubilizes hydrophobic pharmaceutical agents to form a clear solution. The skilled artisan would have had a reasonable expectation of successfully producing a stable, clear film-forming composition comprising the compound of instant formula (I) which provide improved cosmetic and mechanical properties.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gaillard, Partain, Smith, Mougin and Cremophor as applied to claims 1, 2, 4-8, 11-14, 22, 23, 28, 29, 39, 40 and 46 as above, and further in view of Ismail (US 5541220).

The combined references fail to teach methylxanthine compounds.

Ismail teach agents for the treatment protection of the skin. Exemplified is a capsule that can treat alopecia, which comprises pentoxifylline, vitamin E, and other ingredients.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of the combined references by adding pentoxifylline to the composition of the combined references as motivated by Ismail because a) Gaillard and Ismail are directed to treating alopecia; and b) Ismail teach pentoxifylline as increasing blood circulation which is used in an alopecia treatment

composition. The skilled artisan would have had a reasonable expectation of successfully producing an alopecia treatment composition which increases blood circulation and aids circulating the active agents of the composition through the body.

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaillard, Partain, Smith, Mougins and Cremophor as applied to claims 1, 2, 4-8, 11-14, 22, 23, 28, 29, 39, 40 and 46 as above, and further in view of Gaetani et al. (EP 0427625 A).

Gaillard teaches to combine phenylimidazolidines with a product stimulating the growth of hair for the treatment of alopecia. See col. 9, lines 55 – 65. The reference fails to teach 2,4-diamino-6-butoxy-3-sulfoxypyrimidine hydroxide.

Gaetani teaches internal salts of 2,4-diamino-6-alkoxy-3-sulfoxypyrimidine hydroxide for combating hair loss and inducing/stimulating hair growth. See abstract. Specifically disclosed is 2,4-diamino-6-butoxy-3-sulfoxypyrimidine hydroxide. See Example de composition 2 and 3.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of the combined references by adding 2,4-diamino-6-butoxy-3-sulfoxypyrimidine hydroxide to the composition, as motivated by Gaetani because (a) both Gaillard and Gaetani are directed toward combating hair loss; and (b) Gaillard teaches to combine phenylimidazolidines with hair growth stimulating agents to make an anti-alopecia composition. The skilled artisan would

have had a reasonable expectation of successfully producing an improved anti-alopecia composition which combats hair loss and promotes hair growth.

Claims 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaillard, Partain, Smith, Mougin and Cremophor as applied to claims 1, 2, 4-8, 11-14, 22, 23, 28, 29, 39, 40 and 46 as above, and further in view of applicants' own disclosure and Hocquaux et al. (WO 92/21317).

Gaillard teaches to combine phenylimidazolidines with a product which stimulates the growth of hair for the treatment of alopecia. See col. 9, lines 55 – 65. The combined references fail to teach 2, 6-diamono-4-piperidinopyridine.

Hocquaux ('317) teaches compositions containing a pyridine-1-oxide compound for combating hair loss and inducing/stimulating hair growth. See '701, abstract. 2,6-diamino 4-peperdinopyridine 1-oxide is disclosed in Example 1. See instant claims 18 and 20.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of the combined references by adding 2,6-diamino 4-peperdinopyridine 1-oxide to the composition because (a) both Gaillard and Hocquaux are directed toward combating hair loss; and (b) Gaillard teaches to combine phenylimidazolidines with other hair growth stimulating agents to make an anti-alopecia composition. The skilled artisan would have had a reasonable expectation of successfully producing an improved anti-alopecia composition which combats hair loss and promotes hair growth.

Claims 18 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaillard, Partain, Smith, Mougine and Cremophor as applied to claims 1, 2, 4-8, 11-14, 22, 23, 28, 29, 39, 40 and 46 as above, and further in view of Hocquaux et al. (WO 91/19701).

Gaillard teaches to combine phenylimidazolidines with a product stimulating the growth of hair for the treatment of alopecia. See col. 9, lines 55 – 65. The combined references fail to teach 2,6-diamino-4-butoxy-1,3,5-triazine 1-oxide.

Hocquaux ('701) teaches compositions containing 2, 6-diamino-1,3,5-triazine derivatives for combating hair loss and inducing/stimulating hair growth. See abstract. 2,6-diamino-4-butoxy-1,3,5-triazine 1-oxide is disclosed in Examples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of the combined references by adding 2,6-diamino-4-butoxy-1,3,5-triazine 1-oxide to the composition because (a) both Gaillard and Hocquaux are directed toward combating hair loss; and (b) Gaillard teaches to combine phenylimidazolidines with other hair growth stimulating agents to make an anti-alopecia composition. The skilled artisan would have had a reasonable expectation of successfully producing an improved anti-alopecia composition which combats hair loss and promotes hair growth.

Response to Arguments

Applicant's arguments filed February 3, 2010 have been fully considered but they are not persuasive.

Applicant assert the rejection fails to explain why a skilled artisan would have resorted to Mougin which according to applicant does not disclose film-former, plasticizers, active agents or uses of the other cited references. The argument is unpersuasive because the Mougin teaching of using a plasticizer to improve the film properties is not limited to any particular active agent or ingredients. In particular, applicant asserts the cosmetic use of the Mougin products would not have rendered the use of a plasticizer in a pharmaceutical composition. The argument is viewed unpersuasive as a plasticizer is taught as a film softener rather than a delivery vehicle. Regardless of whether the end use of the topical composition is to deliver pigments on skin or pharmaceutical active agent, a person of ordinary skill in the art would have considered the teachings of useful plasticizers in Mougin relevant to the film forming composition art. There is nothing in the references to suggest that a plasticizers used in a cosmetic would not have been operable in a pharmaceutical composition. Furthermore, Mougin examples include mouthwash, deodorant and sun care compositions which are designed to deliver active agents to substrate, therefore the use of a plasticizer in formulations for active ingredients other than antibacterial, antiperspirant or UV-ray screening agent would have been an obvious matter to a skilled artisan.

Applicant also asserts that Mougin fails to define what "cosmetic and mechanical properties" of a film forming composition are improved and fails to explain why such properties would be desirable. Examiner views the argument is not convincing, as a person of ordinary skill in film forming composition art would have

known the term "plasticizer" means a softener, and the references plainly suggests softened rather than brittle or rigid film is preferred for dermatological compositions.

Applicant also remarks that Example 15 of Mougins fails to teach POE hydrolyzed castor oil and Example 16 instead teaches this plasticizer in a mouthwash formula. Examiner acknowledges that the reference to Example 15 was a typographical error, but maintains the position that the use of the plasticizer in a mouthwash formulation would have still rendered the present invention obvious. A mouthwash is a topical product, as the active agents are to be delivered to the mucous membrane of the oral cavity. Furthermore, there is nothing in the reference to suggest that the utility of oxyethylenated castor oil is limited to this particular product. Rather, a person of ordinary skill in the art would have learned from Mougins that POE castor oil is a preferred hydrophilic plasticizer which can be safely used for pharmaceutical compositions.

Applicant also teaches that Mougins is directed specifically to pseudo latex compounds and a skilled artisan would not have had a reasonable expectation to succeed with film forming agents not of pseudo-latex. In response, applicant's independent claim 1, 22, 23, 29, 29 do not define any specific film forming agents other than the agents be physiologically tolerable. With respect to claim 46, at least acrylate copolymers in applicant's Markush group is taught in the Mougins reference. Thus applicant's assertion that the Mougins film formers are different from those used in the present invention is unpersuasive. Nonetheless, Mougins teaches that the utility

of a plasticizer with a film forming composition had been notoriously well known in topical film forming composition art, therefore the rejection is viewed proper.

Applicant also argues that selection of chemical compounds needs a careful consideration, citing the Cremophor pamphlet which states, "Cremophor RH40 may alter the rate of absorption of active substances". However, applicant does not explain why this disclosure would have deterred a skilled artisan to use the advantageous plasticizer which has multiple benefits in a topical composition. The reference teaches that POE castor oil 40 is an excellent choice for topical administration as it has very little odor, and applicable for various oils and drugs and also serves as an emulsifying agent. On the other hand, there is no evidence that modification of absorption of an active agent per se would have rendered a composition inoperable.

Applicant asserts the Office's reasons to combine the references do not apply to claim 23. The argument is unpersuasive because the rejection has discussed Gaillard's teachings that 4-[3-(4-hydroxybutyl)-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile of instant claim 4 is useful for treating alopecia and the suggestion of the reference to combine the active agent with other hair growth promoter, such as Minoxidil (6-amino-4-piperidino-1, 2-dihydro-1-hydroxy-2-iminopyrimidine). See Gaillard, col. 9, lines 56 – 65. Therefore, a person of ordinary skill in the art would have obviously envisioned the use of a film-forming composition of the Gaillard invention in treating alopecia.

For above reason's applicant's arguments are viewed unpersuasive, and the rejections as indicated above are viewed proper.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINA C. YU whose telephone number is (571)272-8605. The examiner can normally be reached on Monday through Thursday, from 8:00AM until 6:00 PM..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GINA C. YU/
Primary Examiner, Art Unit 1611